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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/050,249	03/30/1998	HARUKI OKAMURA	OKAMURA=2B	6601

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EXAMINER	
JIANG, DONG	

ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
02/04/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/050,249	OKAMURA ET AL.	
	Examiner	Art Unit	
	DONG JIANG	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *93,99,100,104,106,107,116,121 and 122* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *93,99,100,104,106,107,116,121 and 122* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's amendment filed on 24 September 2009 is acknowledged and entered. Following the amendment, claims 108, 117 and 120 are canceled, claims 93, 104 and 116 are amended, and the new claims 121 and 122 are added.

Currently, claims 93, 99, 100, 104, 106, 107, 116, 121 and 122 are pending and under consideration.

Declaration

The prior art rejection of claims 93, 99, 100, 104, 106, 107 and 116 under 35 U.S.C. 103(a) as being unpatentable over Nakamura *et al.* (*Infect. Immun.* 61: 64-70, 1993), set forth in the previous Office actions is maintained. The declaration of Dr. Okamura under 37 CFR 1.132 filed on 9/24/09 is insufficient to overcome the rejection for the reasons below.

In the declaration, Dr. Okamura argues that as reported in Nakamura et al., Dr. Okamura and co-authors found a protein factor in mouse sera, which induces a high level of IFN-γ production, however, were unable to obtain the factor in an isolated and purified form and in sufficient yield necessary for identifying it as either a novel substance or IL-12; that as a result of these later studies (following Nakamura et al.), they unexpectedly discovered that mouse liver cells produce the same protein factor (and named it IGIF), and concluded that "The serum factor whose apparent molecular mass was previously found to be 75 kDa by gel filtration was shown to contain the same 18- to 19-kDa IGIF" (item 7, pages 2-5). Dr. Okamura further argues that at the time Nakamura et al. was published, he and co-authors of Nakamura et al. had neither isolated the factor in an isolated and purified form nor identified the factor as a novel substance; that under these circumstances, no researcher would have considered preparing any monoclonal antibody to the factor because 1) he and co-authors had not established a method in Nakamura et al. for providing sufficient amounts of the factor necessary for preparing such a monoclonal antibody; and 2) even if monoclonal antibodies were to be obtained using the factor, nobody could have selected the desired monoclonal antibody to the factor from among the various antibodies to the factor or possible IL-12 (item 8, pages 5-6). Dr. Okamura further argues that

they consistently and diligently continued studying the factor of Nakamura and, prior to the publication of Okamura et al., found that mouse liver cells produce the IGIF, and serve as a cell source for mIL-18/IGIF and we established a technique for producing sufficient amounts of mIL-18/IGIF necessary for preparing the monoclonal antibody of the instant application using recombinant DNA technology with mRNA isolated from mouse liver cells as mIL-18/IGIF-producing cells; and that their finding was the breakthrough or the key to success for obtaining the monoclonal antibody of the instant application (item 9, page 6).

Applicants argument has been fully considered, but is not deemed persuasive because it is largely opinion/conclusion only (such as "under these circumstances, no researcher would have considered preparing any monoclonal antibody to the factor" because he and co-authors had not established a method in Nakamura et al. for providing sufficient amounts of the factor necessary for preparing such a monoclonal antibody; and their finding was the breakthrough or the key to success for obtaining the monoclonal antibody). Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. *In re Pike and Morris*, 84 USPQ 235 (CCPA 1949). Although an affidavit or declaration which states only conclusions may have some probative value, such an affidavit or declaration may have little weight when considered in light of all the evidence of record in the application. *In re Brandstadter*, 484 F.2d 1395, 179 USPQ 286 (CCPA 1973). Further, contrary to applicants argument that in Nakamura et al., the authors were unable to obtain the factor in an isolated and purified form, Nakamura teaches the purification of the factor (title) by different procedures such as ammonium sulfate precipitation, DEAE-sepharose column, ultrogel, phenyl-sepharose column (page 66, 1st column, Figure 1, and Table 1), and gel electrophoresis (page 66, 2nd column, and page 67, Figure 2). Furthermore, contrary to applicants argument that no researcher would have considered preparing any monoclonal antibody to the factor because Nakamura had not established a method for providing sufficient amounts of the factor necessary for preparing such a monoclonal antibody, the prior art has established methods for purifying a serum protein and further identifying the encoding nucleic acid, and recombinant production of the protein. For example, Timmann et al. (*J. Immunol.* 1991, 146(4): 1265-70) teaches isolation of two Factor H related molecules from serum. Using gel electrophoresis (SDS-PAGE) protein band, Timmann was able to sequence the N-terminal portion of the proteins, and further identified cDNA encoding the protein (page 1269,

1st column, the last two paragraphs). Therefore, identifying a cell source producing a serum protein was not the only way for producing sufficient amount of serum proteins, although the technique disclosed in the present application is important for producing sufficient amounts of mIL-18/IGIF.

Withdrawal of Objections and Rejections:

All objections and rejections of claims 108, 117 and 120 are moot as the applicant has canceled the claims.

The rejection of claims 93, 99, 100, 104, 106, 107 and 116 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of applicant's amendment.

The prior art rejection of claims 93, 99, 100, 104, 106, 107 and 116 under 35 U.S.C. 103(a) as being unpatentable over Nakamura *et al.* (*Infect. Immun.* 61: 64-70, 1993) is withdrawn in view of the new ground of rejection, which appears below.

Rejections under 35 U.S.C. 112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 121 and 122 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants have not pointed out, nor can the Examiner locate, the basis in the specification for the kit in the newly added claims.

This is a new matter rejection.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 93, 99, 100, 104, 106, 107 and 116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakamura *et al.* (*Infect. Immun.* 61: 64-70, 1993), and further in view of Campbell, A. (Laboratory Techniques in Biochemistry And Molecular Biology, Volume 13, Chapter 1, pages 1-33, 1984).

The teachings of Nakamura were reviewed in the previous office actions. Nakamura does not teach a monoclonal antibody to the protein factor. Note, Nakamura's protein factor is now known as IL-18 with an amino acid sequence identical to the present SEQ ID NO:2.

Campbell teaches that it is "customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)", that the potential of monoclonal antibodies in the basic research is considerable, and that in principle they can resolve a single protein from a complex mixture or indeed a single epitope responsible for a specific function of a complex macromolecule (page 29, section "Basic research" in particular).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make the antibodies specific to Nakamura's protein factor inducing IFN-γ production because it is desirable and conventional in the art, following the discovery of a new protein, to both clone the genes coding for it and make monoclonal antibodies to it, as indicated by Campbell. Further, the Board of Patent Appeals and interferences has taken the position that once an antigen has been isolated, the manufacture of

monoclonal antibodies against it is *prima facie* obvious. See Ex parte Erlich, 3 USPQ 2d 1011 (PTO Bd. Pat. APP. & Int. 1987), Ex parte Sugimoto, 14 USPQ 2d 1312 (PTO Bd. Pat. APp. & Int. 1990). The person of ordinary skill in the art would have been motivated to make the antibodies for further studying the protein factor since Nakamura indicated that the protein factor induces high levels of IFN-γ, and it will be of interest to compare it with IL-12 (abstract, for example); and reasonably would have expected success because the technique of making monoclonal antibodies to a specific protein is well established and routinely used in the fields.

Applicants argument filed on 24 September 2009 has been fully considered, but is not deemed persuasive for reasons below.

At pages 7-8 of the response, applicants argue that the Okamura reference clearly states that "the factor of 75kDa" disclosed in Nakamura is considered to be a substance which contains "IGIF of 18- to 19-kDa" and "another protein" bound to "IGIF of 18- to 19-kDa", or a substance which exists in an oligomeric form of "IGIF of 18- to 19-kDa"; that if the monoclonal antibody preparation methods, known to public at the time the present invention was made, are applied to "the factor of 75 kDa" of Nakamura, various antibodies may be produced because "the factor of 75 kDa" of Nakamura contains of "IGIF of 18- to 19-kDa" and "another protein" bound to "IGIF of 18- to 19-kDa", and it would require undue experiment to select the antibody; and that that the "IGIF of 18- to 19-kDa" was not known at the time Nakamura was published, therefore, how would one of ordinary skill in the art be able to select a monoclonal antibody which recognizes an unknown protein, i.e., "IGIF of 18- to 19-kDa"? This argument is not persuasive because as indicated in Dr. Okamura's declaration, the later Okamura reference clearly states "the serum factor whose apparent molecular mass was previously found to be 75 kDa by gel filtration was shown to contain the same 18- to 19-kDa IGIF", and teaches that the protein species with a molecular weight of 75 to 80 kDa was reduced to 19 kDa on 0.1% SDS-polyacrylamide gels in the presence of DTT (page 5 of the declaration), indicating the factor of 75kDa" disclosed in Nakamura is a substance which exists in an oligomeric form. Further, monoclonal antibodies made to Nakamura's factor of 75kDa would bind to the later identified factor of 19 kDa as they consist the same molecule.

At pages 9-10 of the response, applicants argue that Nakamura's factor lost its activity in SDS-PAGE, whereas the activity of Okamura's factor was recovered in the extract of SDS-

PAGE gel slices containing an 18-19 kDa peptide; and that it is therefore considered by applicants that it is uncertain whether the factor of 70 to 75 kDa of Nakamura actually contains the "18- to 19-kDa peptide" of Okamura. This argument is not persuasive because in his declaration, Dr. Okamura clearly states "the NH2-terminal amino acid sequence of the re-prepared factor [Nakamura's factor] was determined to be the same as that of IGIF purified from mouse liver extracts. Based on these results, I and my co-authors of Okamura et al. concluded that "The serum factor whose apparent molecular mass was previously found to be 75 kDa by gel filtration was shown to contain the same 18- to 19-kDa IGIF." Therefore, there is no dispute that the factor of 70 to 75 kDa of Nakamura actually contains the "18- to 19-kDa peptide" of Okamura.

Conclusion:

No claim is allowable.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Dong Jiang/
Primary Examiner, Art Unit 1646
1/30/10